

## CLAIMS

1. A ligand screening apparatus which screens for a ligand that binds to a protein when coordinate data of the protein of single chain or plural chains is given, the apparatus comprising:

post-structural-change protein coordinate data selecting unit that effects structural change in consideration of dynamic behavior using induced-fit parameter reflecting induced fit on the coordinate data of protein and selects post-structural-change protein coordinate data;

spatial point designating unit that designates a spatial point at which superposition with the ligand is to be conducted, from the post-structural-change protein coordinate data selected by the post-structural-change protein coordinate data selecting unit;

interaction function calculating unit that calculates an interaction function when the protein and the ligand bind to each other using the spatial point designated by the spatial point designating unit and a ligand coordinate data of the ligand; and

ligand evaluating unit that evaluates the ligand that binds to the protein based on the interaction function calculated by the interaction function calculating unit.

2. The ligand screening apparatus according to claim 1, wherein the interaction function calculating unit calculates the interaction function using Score (i,j) shown in Formula 1.

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$$Sscore(i, j) = \sum_{ij}^{\lambda} \begin{cases} \text{when } i \text{ is not equal to } j \\ \alpha \times \left[ \exp \left\{ -\left( d_{ij}^s - d_{ij}^c \right)^2 \right\} - \beta \right] / \frac{\left( d_{ij}^s + d_{ij}^c \right)^2}{2} \\ \text{when } i \text{ is equal to } j \\ \alpha \times (1 - \beta) \end{cases} \quad [\text{Formula 1}]$$

(wherein  $d_{ij}^s$  is a distance between i-th spatial point and j-th spatial point in the target protein.  $d_{ij}^c$  is an interatomic distance between i-th atom and j-th atom in the compound.  $\alpha$  is a coefficient for making Sscore(i,j) the maximum value when the group of spatial points in the target protein and the compound completely overlap with each other.  $\beta$  is a coefficient for giving a threshold value by which it can be defined as "overlapping")

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3. The ligand screening apparatus according to claim 1 or 2, wherein the interaction function calculating unit further comprises interaction function optimizing unit that carries out optimization so as to make the score of interaction function maximum.

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4. The ligand screening apparatus according to claim 3, wherein the interaction function calculating unit further comprises:

interaction energy optimizing unit that calculates  
5 interaction energy with the protein for the superposed  
ligand after optimization of the interaction function by  
the interaction function optimizing unit, and optimizes  
the interaction energy while finely adjusting conformation  
of ligand 3D structure data.

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5. The ligand screening apparatus according to claim 4, wherein the ligand evaluating unit further comprises:

reevaluating unit that executes the interaction  
function calculating unit after largely changing  
15 conformation of ligand 3D structure data following  
optimization by the interaction energy optimizing unit,  
and reevaluates the ligand that binds to the protein based  
on the interaction function calculated by the interaction  
function calculating unit.

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6. The ligand screening apparatus according to any one  
of claims 1 to 5, wherein in calculation of any one of the  
induced-fit parameter and the post-structural-change  
protein coordinate data or both, the post-structural-  
25 change protein coordinate data selecting unit calculates

normal mode for the protein coordinate data, determines intensity of fluctuation of each amino acid, and conduct molecular dynamic calculation using the intensity of fluctuation as a constraint condition.

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7. The ligand screening apparatus according to claim 6, wherein the post-structural-change protein coordinate data selecting unit calculates a fluctuation value of dihedral angle of main chain according to normal mode calculation, and conducts molecular dynamic calculation while setting the fluctuation value as a coefficient of force K in the molecular dynamic calculation shown by Formula 2 or Formula 3.

$$15 \quad E_{rot} = K_{rot}(\phi - \phi_0)^2 \quad [\text{Formula 2}]$$

(wherein  $E_{rot}$  represents energy of dihedral angle of main chain atom in 3D structure of a protein.  $\phi$  represents dihedral angle of main chain atom.  $\phi_0$  represents standard value of dihedral angle of main chain atom. Here, when a value of  $K_{rot}$  is large,  $\phi$  is constrained by  $\phi_0$ .)

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$$E_{pos} = K_{pos}(r - r_0)^2 \quad [\text{Formula 3}]$$

(wherein  $E_{pos}$  represents position energy of main chain atom in 3D structure of a protein.  $r$  represents

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coordinate of main chain atom. r0 represents standard value of coordinate of main chain atom. Here, when a value of Kpos is large, r is constrained by r0.)

5 8. The ligand screening apparatus according to any one of claims 1 to 7, wherein the interaction function calculating unit uses the interaction function to which a dynamic property function representing dynamic property of protein is added as "elastic energy".

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9. The ligand screening apparatus according to claim 8, wherein the interaction function calculating unit adapts "U collision" as "elastic energy" which is a function shown by Formula 4 in consideration of local flexibility  
15 of protein.

$$U_{\text{collision}} = \sum_{i=1}^M \sum_{j=1}^N \varphi(i, j)$$

$$\varphi(i, j) = K_{\text{collision}} * (R_{\text{collision}}(i, j) - R)^2$$

[Formula 4]

(wherein M is number of atoms in an active site that  
20 prohibit collision, N is number of atoms of ligand. When interatomic distance R between an i-th atom of a main chain or a side chain with a little dynamic behavior in an active site, and j-th atom in the ligand is not more than

collision distance "Rcollision(i,j)",  $\phi(i,j)$  is  
calculated)

10. The ligand screening apparatus according to any one  
5 of claims 1 to 7, wherein the interaction function  
calculating unit uses the interaction function to which a  
normal mode analysis result or secondary structure  
determination result of the protein is added as a dynamic  
property function that represents dynamic property of  
10 protein.

11. A ligand screening method which screens for a ligand  
that binds to a protein when coordinate data of the  
protein of single chain or plural chains is given, the  
15 method comprising:

post-structural-change protein coordinate data  
selecting step that effects structural change in  
consideration of dynamic behavior using induced-fit  
parameter reflecting induced fit on the coordinate data of  
20 protein and selects post-structural-change protein  
coordinate data;

spatial point designating step that designates a  
spatial point at which superposition with the ligand is to  
be conducted, from the post-structural-change protein  
25 coordinate data selected by the post-structural-change

protein coordinate data selecting step;

interaction function calculating step that calculates an interaction function when the protein and the ligand bind to each other using the spatial point designated by the spatial point designating step and a ligand coordinate data of the ligand; and

ligand evaluating step that evaluates the ligand that binds to the protein based on the interaction function calculated by the interaction function calculating step.

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12. The ligand screening method according to claim 11, wherein the interaction function calculating step calculates the interaction function using Score (i,j) shown in Formula 1.

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$$Sscore(i, j) = \sum_{ij}^{\lambda} \begin{cases} \text{when } i \text{ is not equal to } j \\ \alpha \times \left[ \exp \left\{ -\left( d_{ij}^s - d_{ij}^c \right)^2 \right\} - \beta \right] / \frac{\left( d_{ij}^s + d_{ij}^c \right)^2}{2} \\ \text{when } i \text{ is equal to } j \\ \alpha \times (1 - \beta) \end{cases} \quad [\text{Formula 1}]$$

(wherein  $d_{ij}^s$  is a distance between i-th spatial point and j-th spatial point in the target protein.  $d_{ij}^c$  is an interatomic distance between i-th atom and j-th atom in the compound.  $\alpha$  is a coefficient for making Sscore(i,j) the maximum value when the group of spatial points in the

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target protein and the compound completely overlap with each other.  $\beta$  is a coefficient for giving a threshold value by which it can be defined as "overlapping")

5 13. The ligand screening method according to claim 11 or 12, wherein the interaction function calculating step further comprises interaction function optimizing step that carries out optimization so as to make the score of interaction function maximum.

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14. The ligand screening method according to claim 13, wherein the interaction function calculating step further comprises:

interaction energy optimizing step that calculates  
15 interaction energy with the protein for the superposed ligand after optimization of the interaction function by the interaction function optimizing step, and optimizes the interaction energy while finely adjusting conformation of ligand 3D structure data.

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15. The ligand screening method according to claim 14, wherein the ligand evaluating step further comprises:

reevaluating step that executes the interaction  
function calculating step after largely changing  
25 conformation of ligand 3D structure data following



optimization by the interaction energy optimizing step,  
and reevaluates the ligand that binds to the protein based  
on the interaction function calculated by the interaction  
function calculating step.

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16. The ligand screening method according to any one of  
claims 11 to 15, wherein in calculation of any one of the  
induced-fit parameter and the post-structural-change  
protein coordinate data or both, the post-structural-  
10 change protein coordinate data selecting step calculates  
normal mode for the protein coordinate data, determines  
intensity of fluctuation of each amino acid, and conduct  
molecular dynamic calculation using the intensity of  
fluctuation as a constraint condition.

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17. The ligand screening method according to claim 16,  
wherein the post-structural-change protein coordinate data  
selecting step calculates a fluctuation value of dihedral  
angle of main chain according to normal mode calculation,  
20 and conducts molecular dynamic calculation while setting  
the fluctuation value as a coefficient of force K in the  
molecular dynamic calculation shown by Formula 2 or  
Formula 3.

25  $E_{rot} = K_{rot}(\phi - \phi_0)^2$

[Formula 2]

(wherein Erot represents energy of dihedral angle of main chain atom in 3D structure of a protein.  $\phi$  represents dihedral angle of main chain atom.  $\phi_0$  represents standard value of dihedral angle of main chain atom. Here, when a value of Krot is large,  $\phi$  is constrained by  $\phi_0$ .)

$$E_{pos} = K_{pos}(r - r_0)^2 \quad [\text{Formula 3}]$$

(wherein Epos represents position energy of main chain atom in 3D structure of a protein.  $r$  represents coordinate of main chain atom.  $r_0$  represents standard value of coordinate of main chain atom. Here, when a value of Kpos is large,  $r$  is constrained by  $r_0$ .)

18. The ligand screening method according to any one of claims 11 to 17, wherein the interaction function calculating step uses the interaction function to which a dynamic property function representing dynamic property of protein is added as "elastic energy".

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19. The ligand screening method according to claim 18, wherein the interaction function calculating step adapts "U collision" as "elastic energy" which is a function shown by Formula 4 in consideration of local flexibility of protein.

$$U_{\text{collision}} = \sum_{i=1}^M \sum_{j=1}^N \phi(i, j)$$

$$\phi(i, j) = K_{\text{collision}} * (R_{\text{collision}}(i, j) - R)^2$$

[Formula 4]

(wherein M is number of atoms in an active site that  
 5 prohibit collision, N is number of atoms of ligand. When  
 interatomic distance R between an i-th atom of a main  
 chain or a side chain with a little dynamic behavior in an  
 active site, and j-th atom in the ligand is not more than  
 collision distance "Rcollision(i,j)",  $\phi(i,j)$  is  
 10 calculated)

20. The ligand screening method according to any one of  
 claims 11 to 17, wherein the interaction function  
 calculating step uses the interaction function to which a  
 15 normal mode analysis result or secondary structure  
 determination result of the protein is added as a dynamic  
 property function that represents dynamic property of  
 protein.

20 21. A program which makes a computer execute a ligand  
 screening method which screens for a ligand that binds to  
 a protein when coordinate data of the protein of single  
 chain or plural chains is given, the method comprising:

post-structural-change protein coordinate data  
selecting step that effects structural change in  
consideration of dynamic behavior using induced-fit  
parameter reflecting induced fit on the coordinate data of  
5 protein and selects post-structural-change protein  
coordinate data;

spatial point designating step that designates a  
spatial point at which superposition with the ligand is to  
be conducted, from the post-structural-change protein  
10 coordinate data selected by the post-structural-change  
protein coordinate data selecting step;

interaction function calculating step that calculates  
an interaction function when the protein and the ligand  
bind to each other using the spatial point designated by  
15 the spatial point designating step and a ligand coordinate  
data of the ligand; and

ligand evaluating step that evaluates the ligand that  
binds to the protein based on the interaction function  
calculated by the interaction function calculating step.  
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22. The program according to claim 21, wherein the  
interaction function calculating step calculates the  
interaction function using  $\text{Score}(i,j)$  shown in Formula 1.

$$Sscore(i, j) = \sum_{ij}^{\lambda} \begin{cases} \text{when } i \text{ is not equal to } j \\ \alpha \times [\exp \{-(d_{ij}^s - d_{ij}^c)^2\} - \beta] / \frac{(d_{ij}^s + d_{ij}^c)^2}{2} \\ \text{when } i \text{ is equal to } j \\ \alpha \times (1 - \beta) \end{cases} \quad [\text{Formula 1}]$$

(wherein  $d_{ij}^s$  is a distance between  $i$ -th spatial point and  $j$ -th spatial point in the target protein.  $d_{ij}^c$  is an interatomic distance between  $i$ -th atom and  $j$ -th atom in the compound.  $\alpha$  is a coefficient for making  $Sscore(i, j)$  the maximum value when the group of spatial points in the target protein and the compound completely overlap with each other.  $\beta$  is a coefficient for giving a threshold value by which it can be defined as "overlapping")

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23. The program according to claim 21 or 22, wherein the interaction function calculating step further comprises interaction function optimizing step that carries out optimization so as to make the score of interaction

15 function maximum.

24. The program according to claim 23, wherein the interaction function calculating step further comprises:

interaction energy optimizing step that calculates

20 interaction energy with the protein for the superposed

ligand after optimization of the interaction function by

the interaction function optimizing step, and optimizes the interaction energy while finely adjusting conformation of ligand 3D structure data.

- 5    25. The program according to claim 24, wherein the ligand evaluating step further comprises:

reevaluating step that executes the interaction function calculating step after largely changing conformation of ligand 3D structure data following  
10 optimization by the interaction energy optimizing step, and reevaluates the ligand that binds to the protein based on the interaction function calculated by the interaction function calculating step.

- 15    26. The program according to any one of claims 21 to 25, wherein in calculation of any one of the induced-fit parameter and the post-structural-change protein coordinate data or both, the post-structural-change protein coordinate data selecting step calculates normal  
20 mode for the protein coordinate data, determines intensity of fluctuation of each amino acid, and conduct molecular dynamic calculation using the intensity of fluctuation as a constraint condition.

- 25    27. The program according to claim 26, wherein the post-

structural-change protein coordinate data selecting step calculates a fluctuation value of dihedral angle of main chain according to normal mode calculation, and conducts molecular dynamic calculation while setting the

5 fluctuation value as a coefficient of force K in the molecular dynamic calculation shown by Formula 2 or Formula 3.

$$\text{Erot} = \text{Krot}(\phi - \phi_0)^2 \quad [\text{Formula 2}]$$

10 (wherein Erot represents energy of dihedral angle of main chain atom in 3D structure of a protein.  $\phi$  represents dihedral angle of main chain atom.  $\phi_0$  represents standard value of dihedral angle of main chain atom. Here, when a value of Krot is large,  $\phi$  is constrained by  $\phi_0$ .)

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$$\text{Epos} = \text{Kpos}(r - r_0)^2 \quad [\text{Formula 3}]$$

(wherein Epos represents position energy of main chain atom in 3D structure of a protein. r represents  
20 coordinate of main chain atom.  $r_0$  represents standard value of coordinate of main chain atom. Here, when a value of Kpos is large, r is constrained by  $r_0$ .)

28. The program according to any one of claims 21 to 27,  
25 wherein the interaction function calculating step uses the

interaction function to which a dynamic property function representing dynamic property of protein is added as "elastic energy".

- 5 29. The program according to claim 28, wherein the interaction function calculating step adapts "U collision" as "elastic energy" which is a function shown by Formula 4 in consideration of local flexibility of protein.

$$10 \quad U_{\text{collision}} = \sum_{i=1}^M \sum_{j=1}^N \phi(i, j)$$

$$\phi(i, j) = K_{\text{collision}} * (R_{\text{collision}}(i, j) - R)^2$$

[Formula 4]

(wherein M is number of atoms in an active site that prohibit collision, N is number of atoms of ligand. When interatomic distance R between an i-th atom of a main chain or a side chain with a little dynamic behavior in an active site, and j-th atom in the ligand is not more than collision distance "Rcollision(i,j)",  $\phi(i,j)$  is calculated)

- 20 30. The program according to any one of claims 21 to 27, wherein the interaction function calculating step uses the interaction function to which a normal mode analysis result or secondary structure determination result of the



protein is added as a dynamic property function that represents dynamic property of protein.

31. A computer readable recording medium in which the  
5 program according to either of claims 21 to 30 is recorded.